

Review Memo: Biotest AG's Blood Grouping Reagents Anti-S (Monoclonal) and Anti-Jkb (Monoclonal) (12/11/2007) - Seraclone Blood Grouping Reagent Anti-S (Monoclonal)

Date: December 11, 2007

To:

Files of STNs 125216/0 and 125217/0

From:

Teresita C. Mercado, Consumer Safety Officer, Devices Review Branch

Subject:

Review memo: Biotest AG's Blood Grouping Reagents Anti-S (Monoclonal) and Anti-Jk^b (Monoclonal)

Through:

Sheryl A. Kochman, Chief, Devices Review Branch

Background:

Biotest AG, located in Dreieich, Germany submitted these applications for the licensure of Seraclone® Blood Grouping Reagents (BGR) Anti-S (Monoclonal) and Anti-Jk^b (Monoclonal) which are intended for typing blood specimens using manual tube agglutination methods. Seraclone® Blood Grouping Reagents have been distributed worldwide since 1997.

CBER received the original submission dated September 22, 2006 on September 29, 2006. Regulatory documents in the submission include Form FDA 356h, draft labeling, chemistry, manufacturing and controls, establishment information, stability data, and batch records CBER issued a Complete Response (CR) letter to Biotest on July 27, 2007.

This memorandum is a review of the amendment submitted by Biotest in response to the questions and comments conveyed in the CR letter. This memorandum does not address facility-related issues.

both normal blood donors and patients at the test sites except for the OAI testing facility where samples were obtained from normal samples from the Gulf Coast Blood Center.

20 months

Biotest performed additional testing at FDA’s request for Anti-M, Anti-N, Anti-S, Anti-s Anti-Fy^a, Anti-P1, Anti-Le^a, Anti-k, Anti-Jk^a, Anti- Jk^b and Anti-E in the Biotest Diagnostic Corporation facility in the U.S. and the Biotest AG facility in Germany. Immucor reagents were used as reference reagents for the Biotest Anti-S (Monoclonal) and Anti-Jk^b (Monoclonal) reagents.

The table below summarizes the rate of agreement for the Anti-S (Monoclonal) and Anti-Jk^b (Monoclonal) and the reference method.

Combined Rate of Agreement (2006 and 2007 data)

Trial Reagent	Number in Agreement	Number of tests	% Agreement	Lower 95% Confidence Limit
Anti-S (MS 94)	360	360	100%	99.17%
Anti-Jk^b (MS 8)	389	389	100%	99.23%

In addition, testing was performed to meet the following objectives:

- Validate the use of other anti-human globulin reagents with Biotest’s Anti-Fy^a and Anti-s reagents
- Support the use of other anticoagulants other than EDTA
- Determine substances that could interfere with testing
- Support the testing of EDTA and clotted samples up to 10 days old and donor segments up to the unit’s expiration date
- -----

- Obtain data on samples from elderly patients (>80 years old)
- Obtain data on samples with known red blood cell antibodies

Anticoagulant, interfering substances, sample age and sample storage studies were performed on representative products. These representative products were chosen based on the diluents used in the manufacturing of the products.

The results of the studies are summarized below:

Sample Age Study: There were no grouping discrepancies between the Biotest and the reference reagents.

Hemolyzed Samples: There were no grouping discrepancies between the Biotest and the reference reagents. The results prior to and after washing the red blood cells were identical.

Icteric Samples: There were no grouping discrepancies between the Biotest and the reference reagents. The results prior to and after washing the red blood cells were identical.

Lipemic Samples: There were no grouping discrepancies between the Biotest and the reference reagents. The results prior to and after washing the red blood cells were identical.

Fresh and Stored EDTA and Clotted Samples with Reagents Red Blood Cells (RRBC) (Screening/Identification/Anti-Human Globulin): The study demonstrated that Biotest RRBC and Biotest Anti-Human Globulin reagents can be used with fresh and stored ----- EDTA anticoagulated and clotted samples.

Fresh and Stored EDTA, Citrated and Clotted Samples with Blood Grouping Reagents: Testing was performed using representative Biotest reagents, i.e., Anti-K, Anti-D, Anti-C, Anti-c, Anti-k and Anti-Lea. There was one sample tested with Anti-Le^a that gave a discrepant result. Testing with a third method confirmed the positive results obtained with the Biotest reagent. A clotted sample that was also tested with Biotest Anti-Le^a gave a false positive result.

Anti-Human Globulin Anti-IgG Testing of Samples with Known Red Blood Cell Antibodies: Ninety eight of the 101 samples were positive with both the Biotest and reference methods. An Anti-D and an Anti-Le_a were not identified by the Biotest reagent but were identified by the reference method. A sample with a known Anti-Fy^a did not react with either of the Biotest and reference methods. Two samples with Anti-M were identified by the Biotest reagent but were not detected by the reference reagent. The combined rate of agreement of the 2006 and 2007 studies is 99.27% (lower 95% confidence bound).

Anti-Human Globulin Anti-IgG,-C3d; Polyspecific Testing of Samples with Known Red Blood Cell Antibodies: One hundred one samples were tested. One sample with Anti-D, and two samples with Anti-M were not detected by the reference reagent. The combined rate of agreement of the 2006 and 2007 studies is 99.35% (lower 95% confidence bound).

Sample from Patients that are >80 Years Old: Only thirty eight samples could be procured for this study. Testing of the samples with a 2-cell RRBC screen and Anti-Human Globulin Anti-IgG and Anti-Human Globulin Anti-IgG,-C3d; Polyspecific yielded no discrepant results.

Testing of Rare Antisera and Anti-E: The combined rate of agreement (2006 and 2007 data) for each of the rare antisera and Anti-E is >99% (lower 95% confidence bound).

Review of the Responses to the Product-related Questions Conveyed in the CR Letter: Questions and Comments are written to address the sponsor directly. A summary of Biotest's response is indicated by *italicized* text.

CMC/CLINICAL/STATISTICS

1. Please define and specify the range of room temperature in the Standard Operating Procedures. Reference is only made to "RT".

Biotest defines room temperature as -----.

2. The Description of the Container Closure System states that the potency data provides evidence that there are no adverse effects, nor interfering substance that leeches out of the container/stopper system during the prolonged storage interval. Please provide an explanation of how no traces of escaped reagent is determined.

*Biotest stated that the container closure integrity testing included -----
----- Results of the potency, pH and protein testing were within the specifications at all time points.*

3. The submission includes transport stability data that was simulated. Biotest AG should design and perform a shipping study that validates the transport of the product from the manufacturing facility in Germany to the United States end-user.

*Biotest evaluated --- shipments from Germany to the U.S. using -----
----- instead of the packaging material that have been in use for licensed products since 2005. The results demonstrated that the -----
----- is capable of maintaining the temperature of the package contents between -----.* As a result of this evaluation, Biotest will perform a new shipping study and submitted the protocol for the transport validation of diagnostic products for overseas shipment. Biotest USA will perform a second shipping study to validate the shipment of the products from Biotest USA to the customer. Biotest submitted the shipping study protocols.

The protocol includes the evaluation of the temperature loggers in the packages. It does not include performance testing.

Please submit the list of identity tests that you perform for each product and explain how they differentiate the reagents from each other.

There is no specific identity test performed for each product. However, in-process testing is performed at various phases of the manufacturing process to ensure the correct identity of the final container product.

8. Volume I, Summary, Rate of Agreement, pages 7 and 8 of 11. The statistical requirement for equivalence of the trial reagents to the approved reference reagents is that the rate of agreement should be at least 98.5% (95% lower confidence bound). The 95% lower confidence rate of agreement for Anti-S is 98.7% and the 95% lower confidence bound rate of agreement for Anti-Jk^b is 98.9%. Please note that although it is not a requirement, we expect the rate of agreement between the new and the reference reagents to be at least 99% (95% lower confidence bound).

Biotest performed additional testing which when combined with the original field trials resulted in an overall agreement of >99% (LCL).

9. Volume I, Summary, Sensitivity/Specificity, page 9 of 11. Please clarify if you performed a separate study using a gold standard method to determine the sensitivity and specificity of your reagents. If not, please be advised that results of calculations derived from comparison testing with another “imperfect test method” should be described as positive and negative agreements.

Biotest did not perform a separate study using a gold standard.

10. Please clarify if each of the lots used in the field trials was produced from a separate batch of antibody, beginning at the stage of thawing frozen aliquots of the working cell bank as recommended in the March 1992 draft FDA Guidance, Points to Consider in the Manufacture of In Vitro Monoclonal Antibody Products for Further Manufacturing Into Blood Grouping Reagent and anti-Human Globulin.

Biotest was not aware of this recommendation and did not manufacture each of the lots from a separate batch of antibody. Biotest provide a summary of successful production of historic lots to demonstrate Biotest’s experience and expertise in manufacturing these products.

11. Please submit the data that demonstrate the lot-to-lot consistency of each one of the Blood Grouping Reagents. We recommend that you perform a lot-to-lot variability study using at least three (3) lots per reagent. You should obtain data for at least three (3) lots; each of the three lots should have been produced from a separate batch of antibody, beginning at the stage of thawing frozen aliquots of the working cell bank.

Biotest provided data to support the lot-to-lot-consistency of the reagents. These products were not made from separate working cell bank vials but the lots met the potency specifications.

12. Volume I, Investigational Plans, December 2005, Figures 3, 4 and 5, pages 9, 10 and 12. Your criteria for investigating “no type determined” (NTD) does not appear to include the investigation of the cause of the initial NTD if the retest results are concordant. CBER believes that in order to better understand the performance of your reagent, it is important to investigate all NTD and discrepant results including those that are concordant upon retesting. The same rationale can be applied to the red cell typing or antibody identification that had initial discrepant results but were concordant after retesting. Please comment.

Biotest stated that they investigated all NTD and discrepant results. The only NTD results occurred when testing ABO reagents (forward and reverse typing discrepancy) and when testing Anti-D reagents (result of the negative Seraclone ABO/Rh control was positive).

13. Volume I, Investigational Plans, Statistical Analysis, page 22. According to the test protocol, “The rate of agreement will be recalculated after repeat testing, discrepancy resolution, and exclusion of samples associated with a limitation of the reagent or that did not give an interpretation (i.e., due to sample condition or flagged as invalid). This rate of agreement will be compared to the expected results for that sample rather than the reference method.” Since the new test method is being compared to a reference method, the rate of agreement should be based on agreement with the reference method and not the expected results of the sample. You should explain how discrepant results were resolved by a referee method but should not include these in the calculation of the rate of agreement.

According to Biotest, the calculation of the rate of agreement was erroneously stated in the original submission. The calculations were based upon the comparison between the initial test results and the reference test results.

14. Volume I, Investigational Plans, Sensitivity and Specificity for TANGO test components, page 23. The reagents you are seeking licensure for are used for manual techniques. Please explain why the Investigational Plan includes TANGO test components.

The Tango test components were included by mistake.

15. Volume I, Investigational Plans, Records, pages 26 - 28. The Investigational Plan states that the IRB, investigator and sponsor must maintain records for a period of two years after the completion or termination of the investigation. Title 21 CRF 56.115 (b) requires that records and reports be retained for at least 3 years after completion of the research and the records shall be accessible for inspection and

copying by authorized representatives of the Food and Drug Administration at reasonable times and in a reasonable manner. Please comment.

Biotest will retain the records for at least three years after completion of the trial.

16. Volume I, Investigational Plans, Attachment A, IRB Waiver Letter, page 29 and Attachment B, Investigator Agreement, page 30. There is no Attachment A or Attachment B in the submission. Please clarify and submit the documents as necessary.

Biotest submitted the missing documents.

17. Volume I, Clinical Data Sections, page 8. There were only two (2) sites, i.e., University of Virginia and OAI, which performed testing on the rare antisera. Thirty samples were tested at the University of Virginia and 991 samples were tested at the OAI. Please explain your rationale for the limited testing performed on the rare antisera. CBER requires field trial testing in at least one additional site.

Biotest performed additional testing and submitted the data in the response.

18. Volume I, Clinical Data Sections, page 29. Please explain, "Note: The reference methods for the antibody screen are listed in Table I.e. The field trial sites did not match their reference reagents to the trial reagents."

The results listed in Table I.e are for the Biotest Anti-Human Globulin and not for Anti-S and Anti-Jk^b.

19. Volume II, Chemistry, Manufacturing and Control Section, Description of the In Vitro Product, page 6 and Testing Methods and Acceptance Criteria, page 21. The potency titer specification for the Seraclone Anti-Jk^b is ----. Although 21 CFR 660.25 requires a minimum potency of 2+ reaction with undiluted reagent, because of stability concerns, we recommend a minimum potency of 1:8 for monoclonal antibodies as described in *Recommended Methods for Blood Grouping Reagents Evaluation*, Docket No. 84S-0181, dated March 1992.

Biotest changed the potency specification for Anti- Jk^b to ----.

20. Volume II, Chemistry, Manufacturing and Control Section, page 29. This section states, "The Blood Grouping Reagents are tested for specificity and potency using -

-----". These methods are well established and widely accepted standard methods for blood grouping analysis, therefore they do not require method validation." Please note that although these methods are widely used and published, you are required to show that your staff is capable of performing these methods and obtaining correct results consistently in your facility.

You must also include this or a generic description in your package inserts under the Reagents section.

The diluent for Anti-Jk^b is isotonic saline with bovine albumin. The Anti-S diluent is a buffered isotonic saline containing bovine albumin and macromolecular potentiators. The diluents are listed in the reagent package inserts.

27. Volume III, Batch Records. Please clarify if US licensed reagents are used in the in-process and lot release testing of your products. If these reagents are not US licensed, please explain how you qualified the use of these reagents.

U.S. licensed products are not used for in-process testing. Test reagents are tested against a standard which is a current released lot of product. The potency of the reference material is in accordance with 21 CFR 660.25 (a) and CBER's recommended methods.

28. Volume III, Anti-S Monoclonal, Clone Raw Material. Please submit the English translation of these documents, including the translation of the handwritten comments.

Biotest provided the English translation of the documents.

29. Volume III, Anti-S Monoclonal, Batch Records. It appears that you did not provide the English translation of Anlagen 1 zu SV-DS: Q-3042-04. Please review the batch records and submit the English translation of the documents written in German whose English translations have not been submitted.

Biotest provided the English translation of the documents.

30. Volume III, Anti- Jkb Monoclonal, Batch Records, page 98. Please provide the English translation of the handwritten comments next to the labeling.

Biotest provided the English translation of the documents.

31. Volume III, Anti-S Monoclonal, Appendix 15, pages 5 and 6. Please submit the English translation of these documents, including the translation of the handwritten comments.

Biotest provided the English translation of the documents.

32. Please submit the summary of the open stability validation of each of the products.

Biotest provided a copy of the open-vial stability report of each of the products.

LABELING

33. Title 21 CFR 801.437(d) requires the following statement on all labels and labeling for devices that contain natural rubber, "Caution: This product contains Natural Rubber Latex Which May Cause Allergic Reactions."

Biotest has revised the label to include the aforementioned statement.

34. Volume I, DRAFT Labeling, Vial label.

a) Please clarify what the "ACT" on the vial label stands for. "ACT" is not included in the Glossary of Symbols. Moreover, since it is not listed in the FDA Guidance, *Use of Symbols on Labels and in Labeling of In Vitro Diagnostic Devices Intended for Professional Use*, it has to have an English translation on every label (other than the Package Insert [PI]) it appears.

The symbol ACT has been replaced with "Meets FDA Potency Requirements".

b) The symbol you use for preservative is the word PRES in a box. Since it is not listed in the FDA Guidance, *Use of Symbols on Labels and in Labeling of In Vitro Diagnostic Devices Intended for Professional Use*, it has to have an English translation on every label (other than the PI) it appears.

The symbol PRES in a box has been deleted from the vial for lack of space.

c) Please replace "FDA Lic." with "U.S. License" or "U.S. License Number."

"FDA Lic." has been replaced with "U.S. License No."

Because of space limitations, Biotest is requesting an exemption from the requirement of 21 CFR 660.28 (a)(3) that the type size for the specificity of the antibody designation on the labels of the final container with a capacity of less than 5 ml be at least 12 point and the type size for container with a capacity of 5 ml or more be at least 18 point. The type size of Biotest containers with 5 ml and 10 ml capacities is 12 point instead of 18 point.

35. Volume I, Draft Labeling, Carton Label.

a) Please replace “FDA Lic.” with “U.S. License” or “U.S. License Number.”

“FDA Lic.” has been replaced with “U.S. License No.”

b) The symbol you use for preservative is the word PRES in a box. Since it is not listed in the FDA Guidance, Use of Symbols on Labels and in Labeling of In Vitro Diagnostic Devices Intended for Professional Use, it has to have an English translation on every label (other than the PI) it appears.

The symbol PRES in a box has been replaced with the word “Preservative”.

36. Volume, I, Package Inserts, Anti-Jk^a and Anti-Jk^b and Anti-S.

a) Please replace “FDA License” with “U.S. License” or “U.S. License Number.”

“FDA Lic.” has been replaced with “U.S. License No.”

b) For clarity, please replace the word “characteristics” under the Intended Use section with the word “antigen”. The statement should read, “For the determination of the _____ antigen of red blood cells using the tube test.

The word “characteristics” under the Intended Use section has been replaced with the word “antigen”.

c) The Summary section of the Anti-Kidd package insert consists of the following statement: “The Kidd antigen was first identified in 1951 when the corresponding antibody was found to cause hemolytic disease of the fetus and the newborn (HDFN). Although Kidd antibodies have been shown to cause generally mild HDFN, they have been implicated in severe transfusion reactions (HTR). The HTR are often delayed due to an anemnesic response to the Kidd antigen.¹” 21 CFR 809.10 (b)(3) states that the Summary Section (Summary and explanation of the test) must include a short history of the

methodology, with pertinent references and a balanced statement of the special merits and limitations of this method or product. The statement in your package insert does not address this requirement. Please revise the Summary section by adding the required information per 21 CFR 809.10 (b)(3).

Biotest has revised the Summary section to comply with 21 CFR 809.10 (b)(3).

d) The Summary section of the Anti-S package insert consists of the following statement: “Antibodies to the S antigen usually occur following immunization and are capable of causing hemolytic disease of the fetus and the newborn (HDFN) and hemolytic transfusion reactions (HTR).¹” Title 21 CFR 809.10 (b)(3) states that the Summary Section (Summary and explanation of the test) must include a short history of the **methodology**, with pertinent references and a balanced statement of the special merits and limitations of this method or product. The statement in your package insert does not address this requirement. Please revise the Summary section by adding the required information per 21 CFR 809.10 (b)(3).

Biotest has revised the Summary section to comply with 21 CFR 809.10 (b)(3).

e) According to the Specimen collection section, fresh samples of clotted, EDTA or citrate anticoagulated whole blood collected following general blood sampling guidelines are acceptable. However, according to page 20 of the December 2005 Investigational Plan, both patient and donor samples used in the testing will be collected in EDTA. Please submit the data from a study or studies that support the use of the various samples that are acceptable for testing with your reagents as indicated in the labeling. This study should also support the acceptable sample age and storage conditions as stated in the labeling. Please note that samples commonly used in the U.S. include those collected in EDTA, heparin, ACD, CPD, CPDA-1, CP2D and samples without anticoagulant.

*Biotest performed additional testing to collect data on clotted and various anticoagulated samples. See results of the study under **Additional Testing**.*

f) Under “Materials required but not provided”, please specify the dimensions of the tubes that should be used.

Biotest has specified the dimensions of the tubes under the “Materials required but not provided” section.

g) Under “Note”, please replace the statement “Manage waste according to national guidelines” with “Manage waste according to local, state and national regulations”.

Biotest has replaced “Manage waste according to national guidelines” with “Manage waste according to local, state and national regulations”.

h) Glossary of Symbols. Please include “ACT” and its definition in the table. Moreover, since it is not listed in the FDA Guidance, *Use of Symbols on Labels and in Labeling of In Vitro Diagnostic Devices Intended for Professional Use*, it has to have an English translation on every label (other than the PI) it appears.

The symbol ACT has been removed from the labeling and replaced with “Meets FDA Potency Requirements”.

i) -----

-----.

*Biotest opted to remove reference -----
-----.*

j) Title 21 CFR 809.10 (b)(12) requires that the package insert include the specific performance characteristics describing the accuracy, precision, sensitivity and specificity of the product as appropriate. This

section should include a statement summarizing the data upon which the specific performance characteristics are based. You should also include a telephone number that customers can call if additional information regarding testing performed at the time of manufacture is needed.

Biotest has revised the specific performance characteristics section as recommended.

Volume I, Package Insert, Anti-S.

k) Limitation Section. Please include a statement regarding false negative or weakened reactivity if red blood cells are inadvertently exposed to bleach or bleach-containing products.

Biotest has added the aforementioned statement to the Limitation section of the package insert.

Recommendation:

The responses are acceptable except for the following issues:

1. Forms FDA 2567 for the Seraclone® Anti-S container label indicate that this product is ----- monoclonal in origin. Both the container and the package insert indicate that this reagent is human monoclonal in origin. Please clarify and make the necessary corrections.
2. Please revise the lot release protocol template to include the bioburden acceptance criterion and the following information: preservative, cell concentration, suspending medium, serum diluent and temperature.
3. Please submit the results of the shipping studies when completed.